A New Synthetic Route to α-Methylenecarboxamides Using Dianion of N-Phenyl-2-[(phenylsulfonyl) (Commemoration Issue Dedicated to Professor Shinzaburo OKA On the Occasion of His Retirement) methyl] propenamide

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Note

A New Synthetic Route to α-Methylenecarboxamides Using Dianion of N-Phenyl-2-[(phenylsulfonyl)methyl]propenamide

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Regioselective reaction of the dianion of N-phenyl-2-[(phenylsulfonyl)methyl]propenamide with alkyl halides leads to β-substituted carboxamides, which upon Lewis aicd mediated cyclization afford α-methylenecarboxamides in good yields.

KEY WORDS: α-Methylenecarboxamides/ (E)-trisubstituted carboxamides/ 3,4-dihydroxy-2-methylenecarboxamides/ 5,6-dihydro-2*H*-pyrans/ 3-methylene-β-lactams/

The α-methylene carbonyl system is a common structural feature of naturally occuring substances possessing cytotoxic, fungitoxic, and growth-inhibitory activity.[1] Accordingly, various methods have been developed for the synthesis of α-methylene carbonyl derivatives.[2] However, there are relatively few methods available for the direct introduction of α-methylene carbonyl group using a carbanion derived from α-methylene carbonyl system because of the chemical instability of the carbanion.[3] Recently we have found that the dianion of N-phenyl-2-[(phenylsulfonyl) methyl]-propenamide (**1**) can be generated at −78°C and serve as a versatile reagent for the preparation of a variety of α,β-unsaturated carbonyl compounds like (E)-trisubstituted carboxamides, 3,4-dihydroxy-2-methylenecarboxamides, 5,6-dihydro-2*H*-pyrans, and 3-methylene-β-lactams.[4,5]

We now describe a convenient method for the preparation of α-methylene carbonyl derivatives having fused-ring system by regioselective alkylation and subsequent Lewis acid mediated cyclization procedure. The dilithiation of (**1**) proceeds readily with 2 equiv. of butyllithium to provide a yellow solution of (**2**) which can be converted to the β-substituted products (**3**–**7**) upon reaction with alkyl halides. Treatment of the adducts (**3**–**6**) with $AlCl_3$[6] in dichloromethane gives six- or seven-membered exocyclic α-methylene carboxamides (**8**–**11**). On the other hand, reaction of (**7**) with $AlCl_3$ under similar conditions afforded seven-membered endocyclic product (**12**). The endo structure was confirmed by conversion of (**12**) to the known methyl ester (**13**)[7] via isomerization of the double bond of the amide, N-*tert*-butoxycarbonylation, and subsequent methanolysis.[8]

In these synthetic sequences, the amide (**1**) is synthetically equivalent to a 1,1-dipole or a 1,3-dipole (Scheme 3)[6] and perceived as a useful reagent for an efficient

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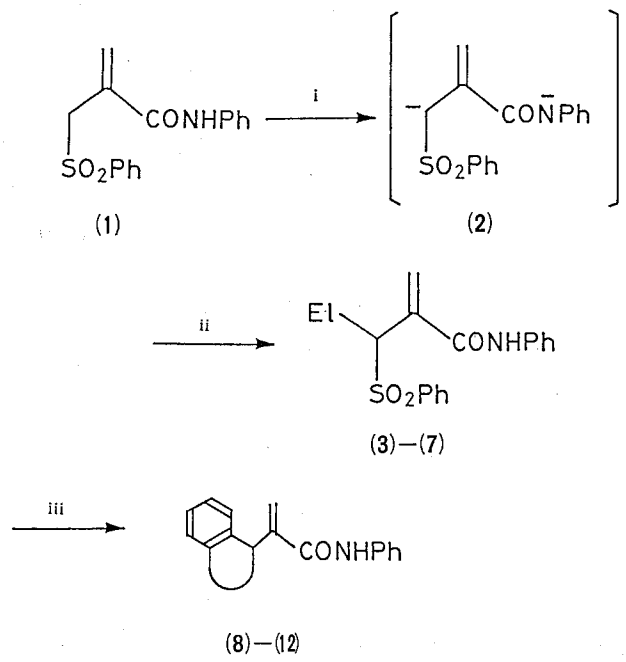
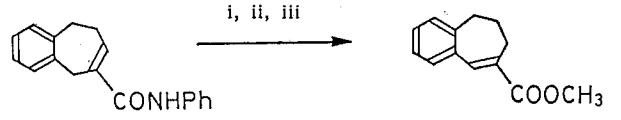


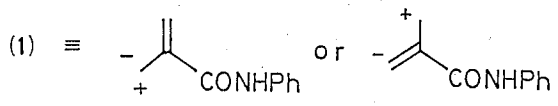
(1) (2) (3)—(7) (8)—(12)

Scheme 1. Reagents and conditions: i, 2 equiv. Bu^nLi, −78°C, Tetrahydrofuran-Hexamethylphosphoric triamide; ii, El-X, −78 to 0°C; iii, $AlCl_3$, dichloromethane.



(12) (13)

Scheme 2. Beagent : i, Bu^tOK ; ii, $(Bu^tOCO)_2O$; iii, CH_3ONa



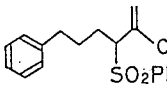
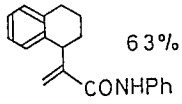
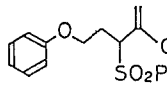
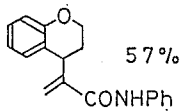
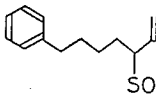
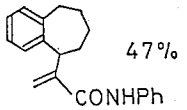
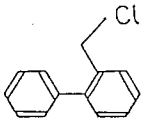
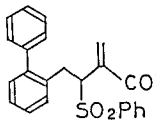
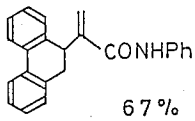
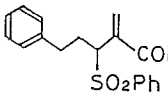
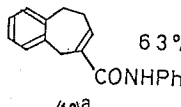
Scheme 3.

elaboration of α-methylene carbonyl derivatives that might otherwise prove difficult to prepare.

EXPERIMENTAL

A typical procedure for the preparation of **3**. To a solution of the dianion **2** (6.64 mmol) at −78°C under argon was added 1-bromo-3-phenylpropane (1.32 g, 6.64 mmol) in dry THF (3 ml). The reaction mixture was stirred at −78°C for 2 h and warmed to 0°C during 1 h, and quenched with saturated aqueous NH_4Cl (10 ml). The product was extracted with ethyl acetate (3×50 ml). The combined

Table 1. Alkylation of dianion (2) and cyclization of adduct.

Halide (El-X)	Adduct	% Yield	Product	% Yield
$Ph(CH_2)_3Br$	 (3)	67%	 (8)[a]	63%
$PhO(CH_2)_2Br$	 (4)	46%	 (9)[b]	57%
$Ph(CH_2)_4Br$	 (5)	76%	 (10)[a]	47%
	 (6)	37%	 (11)[a]	67%
$Ph(CH_2)_2Br$	 (7)	54%	 (12)[a]	63%

a) 3 equiv. $AlCl_3$, dichloromethane, room temp., 1 h.
b) 5 equiv. $AlCl_3$, dichloromethane, reflux, 3 h.

extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by chromatography (silica gel, hexane-ethyl acetate, 3:1) to give 1.87 g of **3** (67% yield): ^1H NMR δ 8.24 (s, 1H), 6.81–7.80 (m, 15H), 6.06 (s, 1H), 5.56 (s, 1H), 4.52 (dd, J=11.0, 4.0 Hz, 1H), 2.32–2.68 (m, 2H), 1.38–2.12 (m, 4H); IR (thin film) 3330, 1608, 1600, 1315, 770, 710 cm^{-1}; exact mass calcd for $C_{25}H_{25}NO_3S$ (M^+) 419.155, found 419.154.

A typical procedure for the conversion of 3 into **8**. To a solution of **3** (0.48 g, 1.15 mmol) in dry CH_2Cl_2 (10 ml) at 0°C under argon was added powdered $AlCl_3$ (0.46 g, 3.45 mmol). After stirring at 0°C for 5 min and at room temperature for 1 h, the reaction mixture was poured into ice water and extracted with CH_2Cl_2 (3×10 ml). The combined extracts were washed with water, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by chromatography (silica gel, hexane-ethyl acetate, 3:1) to give 0.20 g of **8** (85% yield): mp 134–137°C; ^1H NMR δ 7.40–6.80 (m, 10H), 5.87 (s, 1H), 5.05 (s, 1H), 4.20 (m, 1H), 2.78 (m, 2H), 1.40–2.20 (m, 4H); IR (nujol) 3250, 1650, 1600, 760, 700 cm^{-1}. Anal Calcd

for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 81.92; H, 7.07; N, 4.97.

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